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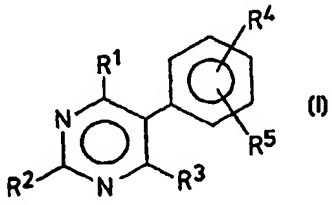
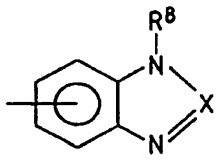
(54) Title: 2,4–DIAMINOPYRIMIDINE COMPOUNDS AS ANTI–CANCER AGENTS



(I)



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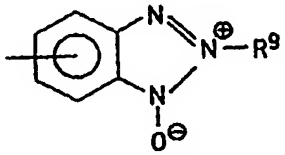

(III)

(57) Abstract

Use of a compound of general formula (I) wherein R^1 and R^2 are independently selected amino groups; R^3 is C_{1-6} alkyl or haloalkyl; R^4 is selected from alkoxy, aralkoxy, haloalkyl, halogen and amino; and R^5 is selected from nitro, amino, azido or a group $-N=X-NR^6R^7$ where R^6 and R^7 are independently C_{1-6} alkyl or are aralkyl or together with the nitrogen to which they are attached form a heterocyclic ring with the proviso that one or both R^6 and R^7 or the heterocyclic ring carries or includes or carries and includes at least one oxygen or sulphur atom, and X is N or CH or CR^9; or R^4 and R^5 together with the benzene ring to which they are attached form a group of formula (II), wherein X is N, CH or CR^9, and R^8 is C_{1-6} alkyl or is aralkyl; or R^4 and R^5 together with the benzene ring to which they are attached form a group of formula (III) wherein R^9 is aryl or aralkyl; or a salt or N–oxide of any such compound, for the manufacture of a medicament for the treatment of mutant–*ras* gene associated cancer.

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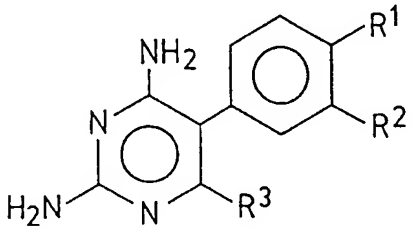
2,4-DIAMINOPYRIMIDINE COMPOUNDS AS ANTI-CANCER AGENTS

This invention relates to the use of 2,4-diaminopyrimidine compounds in the treatment of certain cancers associated with *ras* mutations.

Antifolate agents, such as methotrexate, have been used as antitumour agents for many years and in 1954 metoprine (compound of formula A where R^1=Cl, R^2=Cl, R^3=Me) entered clinical trials.



A

Although severe toxicity associated with this agent precluded further evaluation, the use of pyrimethamine (A, R^1=Cl R^2=H R^3=Et) has been explored and diaminopyrimidine compounds have also been developed which have inherent species selectivity as antibacterial and antimalarial agents.

WO 88/04293 (US 4992444) discloses compounds of this class with inhibition of dihydrofolate reductase (DHFR) comparable to or greater than metoprine but which are relatively less toxic. These compounds are described as of interest as antiproliferative agents useful in the treatment of tumours, psoriasis and bacterial, malarial and trypanosomal infections and are noted to act via DHFR inhibition.

Certain of these compounds were also disclosed as intermediates in WO 84/04746 which relates to azido-substituted pyrimidine derivatives. WO 94/02469 discloses other related compounds, where R^2 is -N=N-NR^8R^9 for use in treatment of *inter alia* AIDS associated infections.

The present inventors have now identified a group of these diaminopyrimidine compounds which have a previously unidentified property in so far as they have activity against mutant-*ras* associated tumours independent of tumour DHFR inhibitor activity.

The Ras, Rho, Rac and Rab proteins make up a large family of monomeric GTPases. The Ras proteins are anchored to the cytoplasmic face of the plasma membrane and relay signals from receptor tyrosine kinases to the cell nucleus in order to stimulate cell proliferation or differentiation.

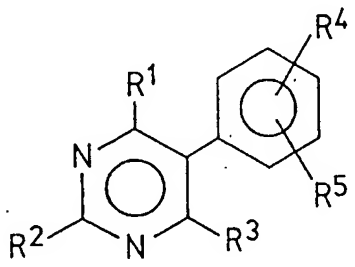
These Ras proteins are produced by *ras* genes, mutants of which promote cancer by disrupting this control of cell proliferation and differentiation. It is believed that about 30% of human cancers involve mutant-*ras* genes. A review of this mechanism by F. McCormick is to found on pages 125-145 of '*Oncogenes and the Molecular Origins of Cancer*' Edited by R. A. Weinberg and published by Cold Spring Harbour Laboratory Press (1989). Further details of the biochemistry of this mechanism are to be found in '*Molecular Biology of the Cell*', by Alberts et al. 3rd Edition (1994) published by Garland Publishing Inc. New York and London; see pages 763-767 and 1276-1289. Other relevant publications include those by Feig., *Journal of the National Cancer Institute* (1993) Vol 85. No 16;1266-1268; Feig and Schaffhausen., *Nature* (1994) 18: 508-9; Mars, *Science* (1993) Vol 260:1588-90; Pretlow et al., *Journal of the National Cancer Institute* (1993) Vol 85 No 24:2004-2007: and Fearon., *Journal of the National Cancer Institute* (1993) Vol 85 No 24:1978-1980.

The prior art ascribes the activity of the aforesaid 2,4-diaminopyrimidine compounds to their dihydrofolate reductase (DHFR) inhibiting activity, and particularly suggests their use in treatment of malignancies of the central nervous system and as antipsoriatic, antibacterial and antimalarial agents. Activity against a wide variety of murine tumour cell lines is demonstrated including lymphocytic leukaemia P388 and L1210, melanotic melanoma B16, colon 38. TLX5 lymphoma, W3129 myeloma, Walker 256 and M5076 reticulum cell sarcoma.

The present inventors have now determined that these compounds have an activity independent of that of their DHFR inhibitor activity which is specific against mutant-*ras* cancer cells and, in particular those of non-small cell lung cancer (NSCL), colon cancer

and pancreatic cancer. Such activity is of particular use where it is suspected or confirmed that a mutant *ras* cancer is present.

Thus, in a first aspect of the present invention there is provided the use of a compound of general formula (I)



(I)

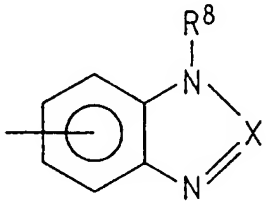
wherein R^1 and R^2 are independently selected amino groups

R^3 is C_{1-6} alkyl or haloalkyl

R^4 is selected from alkoxy, aralkoxy, haloalkyl, halogen and amino and

R^5 is selected from nitro, amino, azido or a group -N=X-NR^6R^7 where R^6 and R^7 are independently C_{1-6} alkyl or are aralkyl or together with the nitrogen to which they are attached form a heterocyclic ring with the proviso that one or both R^6 and R^7 or the heterocyclic ring carries or includes or carries and includes at least one oxygen or sulphur atom, and X is N or CH or CR^9

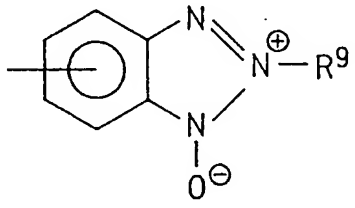
or R^4 and R^5 together with the benzene ring to which they are attached form a group of formula II



(II)

wherein X is N, CH or CR^9, and R^8 is C_{1-6} alkyl or is aralkyl

or R^4 and R^5 together with the benzene ring to which they are attached form a group of formula III



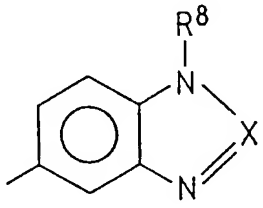
(III)

wherein R^9 is aryl or aralkyl

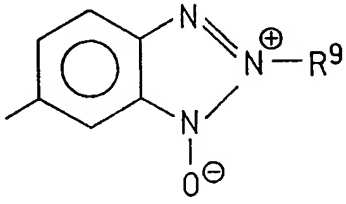
or a salt or N-oxide of any such compound

for the manufacture of a medicament for the treatment of mutant-*ras* gene associated cancer.

More preferably, where R^4 and R^5 form a group of formula II or III with the benzene ring to which they are attached, that group is of formula IV or V



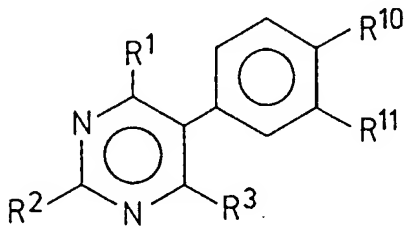
(IV)



(V)

A particularly preferred medicament for which the compounds of formula I may be used in manufacture is for the treatment of mutant-*ras* gene associated cancers selected from non-small lung cell (NSCL), colon and pancreatic cancers, although it will be understood that other forms of mutant-*ras* associated cancer will also be treatable with such compounds.

Particularly preferred compounds for the use of the invention are those of formula VI



(VI)

wherein R^1, R^2 and R^3 are as defined for formula I

R^{10} and R^{11} are selected from haloalkyl, halogen, amino, nitro, azido or a group $-N=X-NR^6R^7$ or, together with the benzene ring to which they are attached, form a group of formula IV or V,

with the proviso that if one of R^{10} and R^{11} is selected from haloalkyl and halo then the other is selected from amino, nitro, azido or a group $-N=X-NR^6R^7$.

or a salt or N-oxide of any such compound.

In all of the formulae I to VI hereinabove the term amino includes primary, secondary, tertiary and quaternary amino groups, but preferred groups are unsubstituted, mono or disubstituted amino groups, including those amino groups forming part of a heterocyclic ring, particularly a ring consisting of from 3 to 7 carbon, nitrogen, sulphur and/or oxygen atoms or as defined for $-NR^6R^7$ above. more preferably being of carbon and nitrogen atoms only. Amino groups are generally substituted by one or two alkyl or aralkyl groups in which the alkyl group or moiety preferably contains 1-6 carbon atoms.

R^1 and R^2 are preferably unsubstituted primary amino groups or secondary or tertiary amino substituted by C_{1-4} alkyl groups.

Where one or more of R^4, R^5, R^{10} or R^{11} is an amino group, the following groups are of particular interest: C_{1-4} alkyl amino, di-C_{1-4}alkyl amino, C_{6-10}aralkyl amino, C_{1-4} alkyl C_{6-10} aralkyl amino, di-C_{6-10} aralkyl amino.

All of the aforesaid groups may be substituted; e.g. by halogen or C_{1-4} alkyl, particularly by chloro. Where the group includes a benzene ring, e.g. an aralkyl amino group, that ring may be substituted one or more times, preferably 1 or 2 times, and most preferably substituted with halogen, e.g. chloro.

Particularly preferred amino groups at R^4, R^5, R^{10} and R^{11} are selected from $-NHCH_3$, $-NHC_2H_5$, $-NH(nC_4H_9)$, $-NHCH_2CH_2Phenyl$, $-NHCH_2Phenyl$, $-N(CH_3)CH_2Phenyl$, $-N(CH_2Phenyl)_2$, $-N(C_2H_5)CH_2Phenyl$ and $-NHCH(CH_3)Phenyl$.

Substituents on aryl rings may conveniently be halogen, C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl, C_{1-6} alkoxy or haloalkoxy, nitro, or $-CO_2R^{12}$ where R^{12} is hydrogen. C_{1-6} alkyl or C_{1-6} alkoxyalkyl. It is found that a $-CONHCH_3$ substitution of these phenyl groups at the 4 position is not desirable as it appears to lead to loss of anti-*ras* activity. However, substitution with halo, e.g. chloro, especially 3.4 dichloro, results in best activity, e.g. see compound 1 of the Examples.

Thus where a group is designated as aralkyl that is preferably a C_{1-4} alkylene group in association with a benzene ring, eg. phenylmethyl, 2-phenylethyl, 3-phenylpropyl or 4-phenylbutyl. Where a group is designated as haloalkyl it is preferably trifluoromethyl.

When R^4 is an alkoxy group it is preferably a C_{1-6}alkoxy group, OCH_3, OC_2H_5 and $O\text{-}nC_4H_9$ being particularly preferred.

The group R^3 is preferably C_{1-6} alkyl. preferably methyl or ethyl.

Most preferred groups R^{10} are mono or disubstituted amino groups such as $-NR^{12}R^{13}$ groups where R^{12} is H or C_{1-4} alkyl and R^{13} is aralkyl, most preferably unsubstituted or halo substituted aralkyl and most particularly R^{10} is $-N(CH_3)CH_2Phenyl$, $-N(CH_3)\text{-}CH_2\text{-}$(3,4 dichloroPhenyl), $-NH\text{-}CH_2\text{-}Phenyl$ or $-NH\text{-}CH_2\text{-}$(3,4-dichloroPhenyl).

R^5, and R^{11}, are most preferably nitro, although azido also leads to good activity. Where one of R^{10} and R^{11} is nitro and the other halogen, particularly chloro, activity is good regardless of position. Similar position independent activity is expected with azido.

The compounds used in the manufacture as described by the present invention are all accessible by methods known in the art with all the examples described herein being known compounds. The compounds described in WO 88/04293 (US 4992444) are cited herein as particular compounds for use in the present manufacture, as are those of WO 94/02469 and WO 84/0446 where they fall within the formula disclosed above. Details of preparative methods for obtaining compounds for use of the invention are to be found in the aforesaid patent documents as well as the following papers: Griffin et al (1985) J. Chem. Soc., Perkin Trans. I :2267; Griffin et al (1989) J. Medicinal Chem 32: 2468-2474; Griffin et al (1990) Anti-Cancer Drug Design, 5: 210-211.

In a second aspect of the present invention there is provided a method of treatment of a patient having mutant-*ras* associated cancer, preferably of the NSCL. colon or pancreatic types, comprising administering to them an effective dose of a compound as described according to formula I or formula VI above.

The amount of these compounds used in the manufacture or method of the invention will of course vary with the type of cancer to be treated and the individual concerned. Dosage forms and route of administration are more fully considered in the PCT application publications referred to above and their associated literature, as are forms such as salts suitable for administration. (See e.g. WO 94/02469 pages 6-9). The corresponding US applications US 4992444 and Serial No 08/374508 are incorporated herein by reference for that purpose and for their teaching of preparation of compounds for use in the method of the invention. The doses of such compounds may be conveniently assessed by reference to the relative efficacy evidenced against *ras* and wild type cancer cells shown in the Examples below.

The present invention will now be illustrated further by reference to the following non-limiting examples. Further embodiments falling within the scope of the invention will occur to those skilled in the art in the light of these.

EXAMPLES

A number of known DHFR inhibitor compounds were selected for screening for anti-tumour activity using the NCI-In Vitro Anticancer Drug Discovery Screen. This is described in detail in a number of publications, particularly by Boyd and Paul in *Drug Development Research* (1995) 34:91-109. These compounds are set out in Table I below in terms of their values R^1 to R^{11} of formula VI. Et in Table 1 represents ethyl.

In brief, the screen measures effect of a given compound on a cell line through to optical density changes which it interprets as changes in percent growth, growth inhibition (GI) and LC_{50}.

Non-small cell lung cancer lines included are A 549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460, NCI-H522. Colon cancer cell lines include COLO-205, HCC-2998, HCT-116, HCT-15, HT-29, KM-12 and SW-620.

On analysis of screening results it was found that the compounds 1 to 13 of Table I above gave the Pearson coefficients shown in Table 2 below as a measure of positive correlation of effect with anti ras-mutant seed cell efficacy for both NSCL and Colon ras types, the results in that table being at Log concentration -4 M. These correlations compare to values of less than 0.3 at the same concentration for a full 59 cell line screen.

The anti-*ras* activity of the compounds for the use of the present invention is illustrated further in Table 3 where individual *ras* v. wild type (Wt) cell efficacies are given and in Table 4 where activity against pancreatic *ras* lines is given.

TABLE 1

Compound	R^1	R^2	R^3	R^{10}	R^{11}
1	$-NH_2$	$-NH_2$	Et	4-(N-(3',4'-dichlorobenzyl)amino)	$3-NO_2$
2	$-NH_2$	$-NH_2$	Et	4-(N-benzyl N-methylamino)	$3-NO_2$
3	$-NH_2$	$-NH_2$	Et	4-Cl	$3-NO_2$
4	$-NH_2$	$-NH_2$	Et	$4-NO_2$	3-Cl
5	$-NH_2$	$-NH_2$	Et	formula V where R^9 is phenyl	
6	$-NH_2$	$-NH_2$	Et	4-Cl	$3-N_3$
7	$-NH_2$	$-NH_2$	Et	4-N-methylamino	$3-NO_2$
8	$-NH_2$	$-NH_2$	Et	4-N-(2-phenylethyl)amino	$3-NO_2$
9	$-NH_2$	$-NH_2$	Et	4-(4-methylpiperazin-1-yl)	$3-NO_2$
10	$-NH_2$	$-NH_2$	Et	4-Cl	$3-N=CH-NMe_2$
11	$-NH_2$	$-NH_2$	Et	4-N-benzylamino	$3-NO_2$
12	$-NH_2$	$-NH_2$	Et	formula IV wherein X is N	and R^8 is benzyl
13	$-NH_2$	$-NH_2$	Et	$4-NO_2$	3-N-benzylamino
14	$-NH_2$	$-NH_2$	Et	$4-NO_2$	3-(N-benzyl,N-methylamin
15	$-NH_2$	$-NH_2$	Et	4-Cl	$3-NH_2$

TABLE 2

PARTIAL RAS SEED - NSCL AND COLON

POSITIVE CORRELATION IS FOR RAS MUTANT SEED CELLS

WITH SENSITIVE CELLS FROM DATABASE

	LCONC	UNITS	MAX X	PEARSON CORR. COEFF.	N
1	-4.00	M	3	0.79	16
2	-4.00	M	3	0.761	16
3	-4.00	M	3	0.755	16
4	-4.00	M	3	0.732	16
5	-4.00	M	3	0.732	16
6	-4.00	M	4	0.723	16
7	-4.00	M	3	0.701	16
8	-4.00	M	3	0.698	16
9	-4.00	M	3	0.697	16
10	-4.00	M	2	0.655	16
11	-4.00	M	3	0.579	16
12	-4.00	M	3	0.557	16
13	-4.00	M	3	0.503	16

TABLE 3

GI_{50} values (μM)*								
		Comp 1	Comp 2	Comp 3	Comp 4	Comp 5	Comp 6	Comp 7	Comp 8
Cell lines †	(PCC)	(0.79)	(0.761)	0.755)	(0.732)	(0.732)	(0.723)	(0.701)	(0.698)
NSCL									
	A549/ATCC	<0.01	<0.01	<0.01	0.097	0.68	0.81	0.24	0.079
Mutant	HOP 62	0.059	0.22	0.49	3.7	9.3	10.0	3.39	1.58
Ki ras	NCI-H23	0.016	0.18	0.06	0.78	2.29	4.17	0.62	0.56
	NCI-H460	<0.01	<0.01	<0.01	0.078	0.44	0.59	0.12	0.043
	EKVX	1.78	3.16	1.8	1.8	12.3	3.55	15.5	5.50
	HOP-92	1.55	1.78	1.7	7.76	11.5	10.7	4.57	4.17
Wt ras	NCI-H266	-	12.3	45.7	19.0	29.5	33.9	42.7	4.57
	NCI-H322M	0.07	2.1	0.34	3.2	3.3	6.9	0.89	0.97
	NCI-H522	0.51	-	-	2.40	3.89	5.75	1.35	1.23
Colon									
	HCT-116	<0.01	<0.01	0.01	0.095	0.56	0.81	0.26	0.051
Mutant	HCT-15	-		0.025	0.06	0.79	0.98	0.32	0.083
Ki ras	SW 620	<0.01	<0.01 0.028	0.033	0.52	0.74	0.98	0.30	0.089
	COLO-205	1.07		5.2	6.3	5.37	10.7	0.78	0.79
Wt ras	HCC-2998	0.14	0.6	0.26	8.9	4.17	4.90	1.20	0.95
	HT-29	<0.01	0.12	0.06	0.56	1.73	3.16	0.46	0.22
	KM-12	0.024	0.025 0.55	0.65	1.95	9.55	6.6	4.90	1.58
Mean GI_{50}	(Full Cell Panel)	0.07	0.025	0.43	8.7	3.89	5.37	1.62	0.85

* 2 day assay. † Ras status from Han-Mo Keo *et al.*, Cancer Research, 1996, 56, 5211-5216

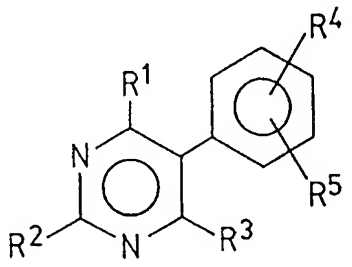
TABLE 4

Activity of compounds agaisnt the pancreatic tumour cell line M1 - mutant Ki-Ras gene 7 day assay.

Compound	IC_{50} (μM)	n
2	11.0	
	13.0	
	12.7	
	26.6	4
2 (methane sulphonic acid salt)	12.6	
	13.4	
	13.5	
	32.6	4
3	43.6	
	63.5	2
7	8.0	
	16.5	2
15	20.5	
	42.75	2
Methotrexate (reference compound)	60.0	
	>100	
	89.0	3
Doxorubicin (reference compound)	0.21	1

CLAIMS

1. Use of a compound of general formula (I)



(I)

wherein

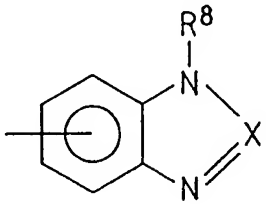
R^1 and R^2 are independently selected amino groups

R^3 is C_{1-6} alkyl or haloalkyl

R^4 is selected from alkoxy, aralkoxy, haloalkyl, halogen and amino and

R^5 is selected from nitro, amino, azido or a group -N=X-NR^6R^7 where R^6 and R^7 are independently C_{1-6} alkyl or are aralkyl or together with the nitrogen to which they are attached form a heterocyclic ring with the proviso that one or both R^6 and R^7 or the heterocyclic ring carries or includes or carries and includes at least one oxygen or sulphur atom, and X is N or CH or CR^9

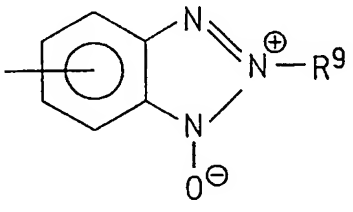
or R^4 and R^5 together with the benzene ring to which they are attached form a group of formula II



(II)

wherein X is N, CH or CR^9, and R^8 is C_{1-6} alkyl or is aralkyl

or R^4 and R^5 together with the benzene ring to which they are attached form a group of formula III



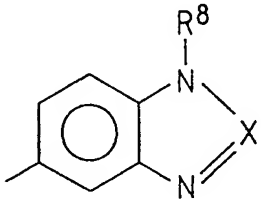
(III)

wherein R^9 is aryl or aralkyl

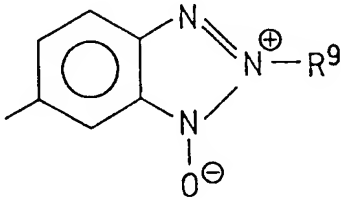
or a salt or N-oxide of any such compound

for the manufacture of a medicament for the treatment of mutant-*ras* gene associated cancer.

2. Use as claimed in claim 1 characterised in that R^4 and R^5 form a group of formula II or III with the benzene ring to which they are attached and that group is of formula IV or V



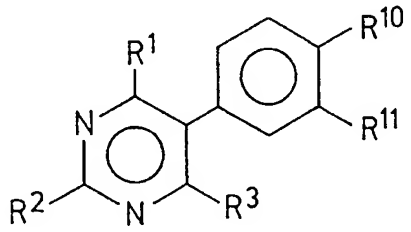
(IV)



(V)

3. Use as claimed in claim 1or 2 characterised in that the medicament manufactured is for the treatment of mutant-*ras* gene associated cancers selected from non-small lung cell (NSCL), colon and pancreatic cancers.

4. Use as claimed in any one of claims 1 to 3 characterised in that the compound is of formula VI



(VI)

wherein R^{10} and R^{11} are selected from haloalkyl, halogen, amino, nitro, azido or a group -N=X-NR^6R^7 or, together with the benzene ring to which they are attached, form a group of formula IV or V,

with the provisio that if one one of R^{10} and R^{11} is selected from haloalkyl and halo then the other is selected from amino, nitro, azido or a group -N=X-NR^6R^7.

or a salt or N-oxide of any such compound.

5. Use as claimed in any one of the preceding claims characterised in that the amino groups are selected from unsubstituted, mono and disubstituted amino groups, including those amino groups forming part of a heterocylic ring.

6. Use as claimed in claim 5 characterised in that the amino group comprises part of a ring consisting of from 3 to 7 carbon, nitrogen, sulphur and/or oxygen atoms.

7. Use as claimed in claim 6 characterised in that the ring is of carbon and nitrogen atoms only.

8. Use as claimed in any one of the preceding claims characterised in that when R^4, R^5, R^{10} or R^{11} are amino groups they are independently selected from C_{1-4} alkyl amino, di-C_{1-4} alkyl amino, C_{6-10} aralkyl amino, C_{1-4} alkyl C_{6-10} aralkyl amino or di-C_{6-10} alkyl amino.

9. Use as claimed in claim 8 characterised in that when R^4, R^5, R^{10} or R^{11} are aralkyl amino groups they are halo substituted on the phenyl ring.

10. Use as claimed in any one of the preceding claims characterised in that when R^4, R^5, R^{10} or R^{11} are amino, one or more of them are independently selected from $-NHCH_3$, $-NHC_2H_5$, $-NH(nC_4H_9)$, $-NHCH_2CH_2Phenyl$, $-NHCH_2Phenyl$, $-N(CH_3)CH_2Phenyl$, $-N(CH_2Phenyl)_2$, $-N(C_2H_5)CH_2Phenyl$ and $-NHCH(CH_3)Phenyl$.

11. Use as claimed in claim 10 characterised in that the aryl group, if present, is substituted by halogen, C_{1-6} alkyl or haloalkyl, C_{2-6} alkenyl or haloalkenyl, C_{1-6} alkoxy or haloalkoxy, nitro, or $-CO_2R^{12}$ where R^{12} is hydrogen alkyl or alkoxyalkyl or C_{1-6}.

12 Use as claimed in any one of the preceding claims characterised in that R^5 or R^{11}, is nitro or azido and R^4 or R^{10} is amino.

13. Use as claimed in any one of the claims 4 to 12 characterised in that one of R^{10} and R^{11} is nitro or azido and the other is halogen.

14. Use as claimed in claim 1 characterised in that the compound is one of

2,4-Diamino-5-[4-(3,4-dichlorobenzylamino)-3-nitrophenyl]-6-ethylpyrimidine,

2,4-Diamino-5-[4-benzylamino-3-nitrophenyl]-6-ethylpyrimidine,

2,4-Diamino-5-[4-chloro-3-nitrophenyl]-6-ethylpyrimidine,

2,4-Diamino-5-[4-nitro-3-chlorophenyl]-6-ethylpyrimidine

2,4-Diamino-5-[4-chloro-3-azidophenyl]-6-ethylpyrimidine, and

2,4-Diamino-5-[4-N-methylamino-3-nitrophenyl]-ethylpyrimidine.

15. A method of treatment of a patient having mutant-*ras* associated cancer comprising administering to them a compound as defined according to formula I or formula VI above.

16. A method as claimed in claim 12 wherein the cancer is of the NSCL, colon or pancreatic types.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/GB 98/00111

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/48 C07D403/04 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 88 04293 A (STEVENS,GRIFFIN) 16 June 1988 cited in the application see the whole document ---	1,3-13, 16
X	WO 84 04746 A (ASTON) 6 December 1984 cited in the application see the whole document ---	1,3-13, 16
X	GB 2 268 741 A (BRTISH TECHNOLOGY GROUP) 19 January 1994 cited in the application see the whole document ---	1,3-13, 16
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of theinternational search	Date of mailing of the international search report
2 April 1998	14.04.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/00111

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	E.BLISS,R.GRIFFIN: "STRUCTURAL STUDIES ON BIO-ACTIVE COMPOUNDS.PART 5." JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1., no. 10, 1987, LETCHWORTH GB, pages 2217-2227, XP002043859 see the whole document	1,3-13, 16
X	CHEMICAL ABSTRACTS, vol. 108, no. 1, 1988 Columbus, Ohio, US; abstract no. 142960k, STEVENS,GRIFFIN: "THE AROMATIC AZIDO GROUP IN ANTICANCER DRUG DESIGN." page 31; column 2; XP002043860 see abstract & ANTICANCER DRUG DESIGN, vol. 2, no. 3, 1987, ENGL., pages 311-318,	1,3-13, 16
X	CHEMICAL ABSTRACTS, vol. 110, no. 7, 1989 Columbus, Ohio, US; abstract no. 50642w, F.KAMALI ET AL.: "MEDICINAL AZIDES.PART 3." page 8; XP002043861 see abstract & XENOBIOTICA, vol. 18, no. 10, 1988, ENGL, pages 1157-1164,	1,3-13, 16

1

INTERNATIONAL SEARCH REPORT

I :ational application No.
PCT/GB 98/ 00111

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3 [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

I. national Application No
PCT/GB 98/00111

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8804293 A	16-06-88	DE 3786256 A	22-07-93
		DE 3786256 T	07-10-93
		EP 0290558 A	17-11-88
		GB 2204867 A,B	23-11-88
		JP 1501477 T	25-05-89
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		EP 0147443 A	10-07-85
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		NZ 253753 A	28-10-96
		US 5618928 A	08-04-97
		ZA 9305010 A	12-01-95